View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Digital Repository @ Iowa State University

IOWA STATE UNIVERSITY
Digital Repository

Creative Components

Iowa State University Capstones, Theses and Dissertations

Spring 2019

Glucocorticoid use in Sports and Exercise

Brett Barthman
Iowa State University, barthman@iastate.edu

Follow this and additional works at: https://lib.dr.iastate.edu/creativecomponents

 Part of the Chemical Actions and Uses Commons

Recommended Citation

Barthman, Brett, "Glucocorticoid use in Sports and Exercise" (2019). *Creative Components*. 135.
https://lib.dr.iastate.edu/creativecomponents/135

This Creative Component is brought to you for free and open access by the Iowa State University Capstones, Theses and Dissertations at Iowa State University Digital Repository. It has been accepted for inclusion in Creative Components by an authorized administrator of Iowa State University Digital Repository. For more information, please contact digirep@iastate.edu.

Glucocorticoid use in sports and exercise

Abstract: *Glucocorticoids (a subclass of the steroid family) have a broad range of therapeutic uses in human and veterinary medicine. Glucocorticoids are widely used to treat sport related/induced injury due to their anti-inflammatory and analgesic effects that allow athletes to resume physical activity, whether competitive sports or personal exercise, in a shorter time after injury. They can also be used to aid recovery after traumatic surgery such as repairing torn ligaments or ruptured tendons. Their route of administration varies from subcutaneous injections to inhalation to injections into intra-articular spaces between bones. New studies have pointed to their possible duel benefits of anti-inflammatory as well as promotion of weight loss through gluconeogenesis. The negative consequences of their use can be controversial due to their widespread popularity as a treatment option in both athletes and routine patients. This paper will discuss the mechanism of action, clinical uses and possible side effects associated with glucocorticoid use in the sport and exercise setting.*

Introduction:

Glucocorticoids are part of a larger family of steroids called corticosteroids which also include mineralocorticoids. Almost all of glucocorticoid activity in most mammals is a result of cortisol, or hydrocortisone, while rodents have corticosterone. The body naturally produces these compounds from the zona fasciculata of the adrenal cortex. Their release is controlled by adrenocorticotropic hormone (ACTH) released from the anterior pituitary. ACTH will then bind to receptors located in the plasma membrane of cells located in zona fasciculata. This results in activation of the enzyme adenylyl cyclase which elevates levels of cyclic AMP in the cell. This cascade activates enzymes which catalyze the synthesis of cortisol from pregnenalone as described in *Figure 1*. Due to the central nervous system controlling ACTH secretion through corticotropin-releasing hormone (CRH), physical or mental stress can result in an increased release of cortisol into the blood. Suppression of cortisol secretion is regulated through a negative feedback loop when levels of cortisol in the blood are too high; elevated cortisol concentrations inhibit the secretion of CHR which in turn decreases ACTH release.

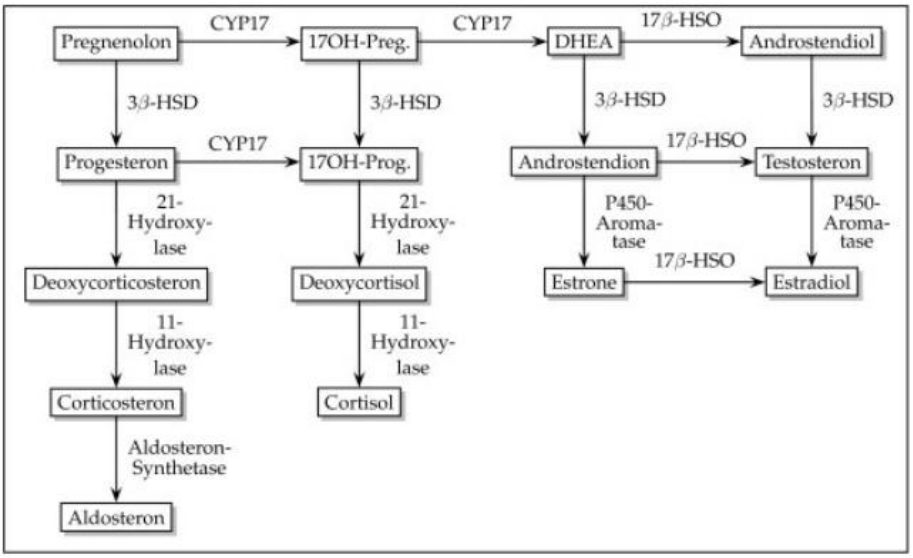

Figure 1. The above diagram shows pregnenalone, synthesized from cholesterol, as a precursor to the biosynthesis of cortisol through multiple enzymatically catalyzed steps. 3β/17β-Hydroxysteroid dehydrogenase (3β/17β-HSD)

Diseases can result where cortisol levels become too high causing hyperadrenocorticism also known as Cushing's disease. This can result from excess systemic production or excess administration for therapeutic purposes. The resulting disease can lead to effects on organ function and metabolism resulting in obesity, muscle wasting, thin skin, and hypertension. Contrary to hyperadrenocorticism is hypoadrenocorticism or Addison's disease where the levels of cortisol are too low. Infectious disease or autoimmune breakdown of the adrenal cortex is the main cause. Symptoms include weakness, diarrhea, and cardiovascular disease. When at proper physiological levels, glucocorticoids have many functions throughout the body. In a fasted state, cortisol increases and maintains glucose levels in the blood through multiple mechanisms. It can increase gluconeogenesis in the liver resulting production of glucose from amino acids and lipids mobilized from extrahepatic tissues. Cortisol can also inhibit the uptake of glucose in adipose and muscle tissue while simultaneously stimulating fat breakdown in adipose tissue. Along with metabolism, glucocorticoids play multiple roles in fetal development including lung maturation and development of cognitive function. Not all roles are positive however, glucocorticoids can cause inhibition of bone formation through inhibition of osteoblasts and delay of wound healing.

Still, due to their desired effects in the treatment of injury, they are synthetically made and administered in our healthcare system today to treat numerous conditions while preventing the onset of others. They are sub-classified into groups based on their application or chemical structure. Applications

are numerous and vary depending on need of the patient, with the glucocorticoids being used to treat conditions as diverse as asthma, inflammation from a chronic Osteoarthritis (OA) and even certain brain tumors. Their mechanism of action can result in anti-inflammatory, anti-pyretic, anti-hyperalgesia and immune suppression.

In patients suffering from brain tumors, glucocorticoids can be used as a course of treatment due to their anti-edema effects and ability to cross the blood-brain-barrier. Dexamethasone is the predominate corticosteroid used for treatment of symptomatic peritumoral edema and malignant brain tumors. Though the proposed mechanisms are widely studied and mostly known for glucocorticoid use systemically, the mechanism of action of corticosteroids on brain tumors is greatly speculated and remains mostly unresolved. Some suggest that their anti-edema effect is accomplished through decreasing the permeability of the capillaries in the tumor. The tight junction (TJ) component in endothelial cells can be upregulated by corticosteroids lowering the endothelial permeability of the capillaries. They can also dephosphorylate occludin and ZO1 which is another TJ component.

In patients suffering from asthma, glucocorticoids can be given systemically or by inhalation. Systemic use is given orally or an intravascular (IV) administration with no difference in results seen between the two routes. Their general effects are exerted on lung epithelial cells inhibiting expression of certain pro-inflammatory mediators and cytokines such as activating protein-1 (AP-1) and cyclo-oxygenase-2 (COX-2). These are well known causes of lung inflammation in certain asthma types.

Here we focus on the use of glucocorticoids in human sport and exercise and how they can be used as a treatment and in preventive medicine.

Modes of action

Anti-inflammatory

Glucocorticoids effect on the anti-inflammatory pathway involves activation of the cytoplasmic glucocorticoid receptor (GR), a 777 amino acid protein that is present in almost every human cell. It is divided into three separate regions with individual functions as seen in *Figure 2*. The first region, also called the N-terminal domain (NTD), has the ligand-independent constitutive transcriptional activation function 1 (AF1). AF1 is responsible for maximal transcriptional activation of the GR. The middle region, also called the DNA-binding domain (DBD), is composed of two conserved finger-like projections of zinc

held by four separate cysteine residues. The first projection contains the contents responsible for recognition of the GREs. The second projection has a region called the distal box responsible for GR homodimerization of the GRE. The final region, also called the ligand-binding domain (LBD), is separated from the DBD by a hinge region providing flexibility of the structure. The LBD contains facilitates in interactions with coregulators, co-chaperones, and other transcriptional factors.

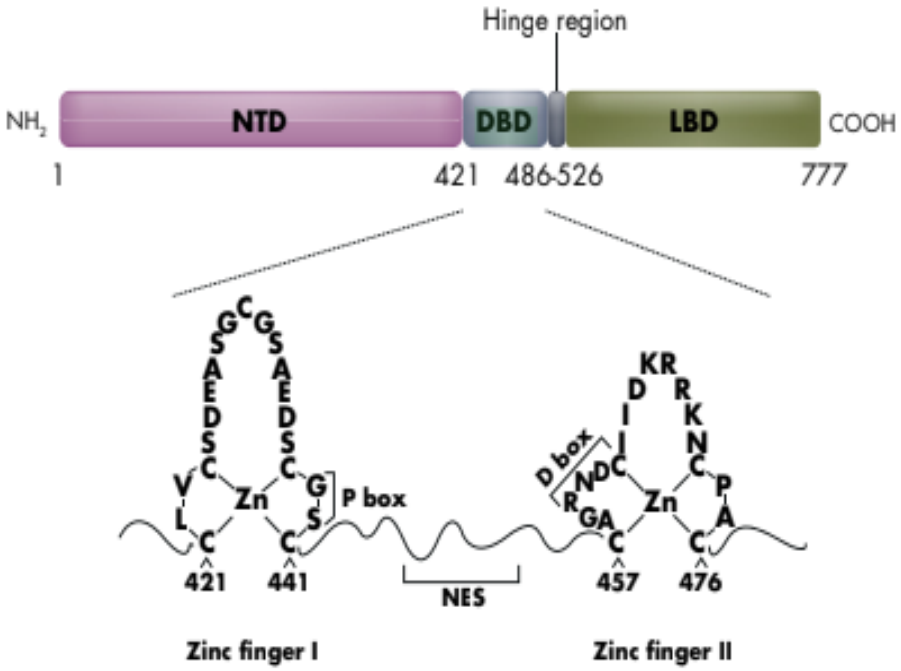

Figure 2. The above figure represents the glucocorticoid receptor (GR) and its three different regions allowing for binding of the glucocorticoid. The N-terminal domain (NTD) has the activation factor (AF1). The DNA-binding domain (DBD) has two separate zinc fingers. The last region called L-binding domain completes the 777 amino acid receptor.

Binding of the glucocorticoid to the intracellular receptor results in a majority of the effects produced as seen in *Figure 3.* When not bound to the steroid, the GR are bound to proteins for stabilizing including immunophilin and heat-shock protein 90 (Hsp90). These receptors are unable to affect gene transcription. Glucocorticoid binding to the GR causes a conformational change in the GR leading to either transactivation or transrepression.

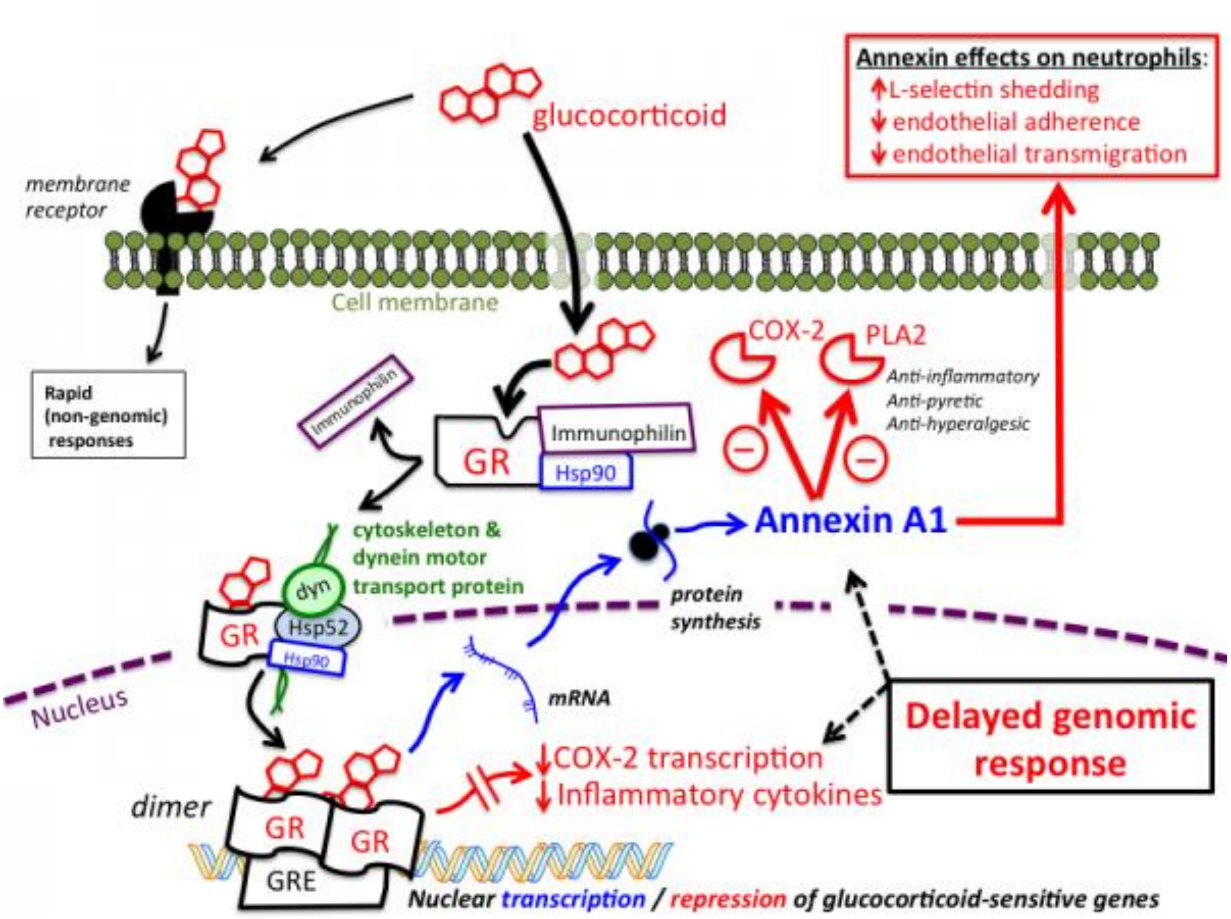

Figure 3. Glucocorticoid intracellular actions post-bound to receptor. The figure above displays the glucocorticoid actions intracellularly and the inhibitory effects on cyclo-oxygenase-2 (COX-2) and phospholipase 2 (PLA2). This leads to decreasing inflammation (anti-inflammatory), reducing fever (anti-pyretic), and lowering sensitivity to pain (anti-hyperalgesia). Dyn (dynein motor transport protein), GR (glucocorticoid receptor), Hsp (heat shock protein)

In **transactivation**, the glucocorticoid-GR complex use translocation via the dynein protein trafficking pathway to move to the nucleus. At the nucleus, the complex activates gene transcription after dimerizing and binding to certain responsive DNA elements called glucocorticoid response elements (GREs) seen in *Figure 3*. These include lipocortin I and p11/calpactin binding protein who are both responsible for suppressing the release of arachidonic acid. B2-adrenoreceptors, decoy IL-1 type II receptor, and secretory leukocyte protease inhibitor (SLPI) are up-regulated but are slower than the lipocortin I and p11/calpactin mechanism at around 24-48 hours. These are responsible for the long-term anti-inflammatory effects resulting somewhat in the reduction of inflammatory cytokines produced but mainly an increase in the synthesis of annexin A1 (*Figure 3)*. This leads to decreased rolling adhesion and transmigration of the neutrophils on the endothelium.

The second pathway, **transrepression**, binds to other transcription factors, negative GRE sites (nGREs), repressing their respected target genes from being activated. It accomplishes this through DNA and non-DNA binding. When bound to DNA, the glucocorticoid-glucocorticoid receptor complex targets the hypothalamic-pituitary-adrenal (HPA) axis repressing adrenocorticotropic hormone (ACTH). This is accomplished using the precursor gene pro-opiomelanocortin (POMC) and corticotropic-releasing hormone (CRH) activation. The GR bind to an nGRE causing repression of transcription through either interactions between proteins and factors on POMC promotor or steric hindrance. Another gene that is repressible by glucocorticoids is the glycoprotein hormone α subunit. The cAMP response element binding protein (CREB) positively regulates this gene and blocks it via DNA binding. This allows the GR to inhibit transcriptional activation. In non-DNA binding, nuclear factor-kB (NF-kB) and activating protein-1 (AP-1) transcriptionally regulate the repression of inflammatory genes by glucocorticoids. NF-kb and AP-1 are responsible for many important biological and pathological functions in the body. Other mechanisms used to account for nGRE sites not usually found in promotors of inflammatory genes.

Glucocorticoids also repress transcriptional activation of these factors. It can bind to AP-1 functionally repressing AP-1 and GR dependent transcription. The same mechanism is proposed for NF-kB.

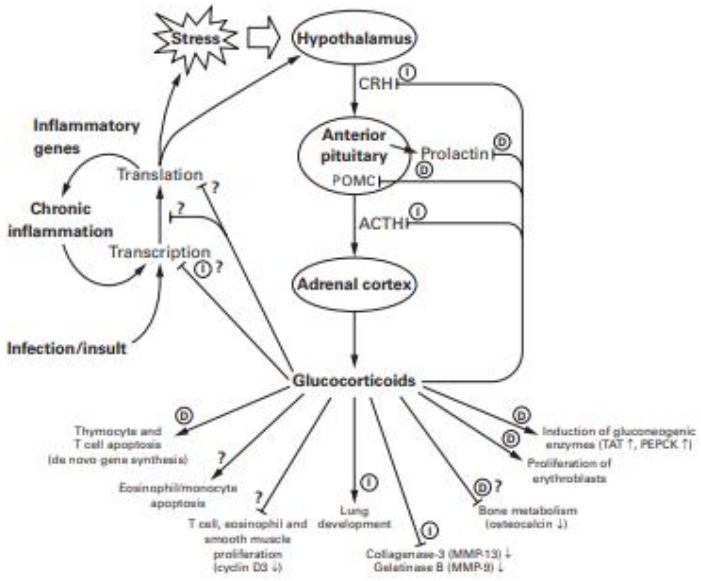

Figure 4. Glucocorticoid effects on the hypothalamic-pituitary-adrenal (HPA) axis.
The above figure displays the synthesis site and action site of the common hormones of the HPA axis and the targets of many glucocorticoid actions. Glucocorticoid effects are labelled as independent (I) or dependent (D) of based off analysis of dimerization defective mice.

Immune suppression

Glucocorticoids suppress the immune system by destroying eosinophils and T lymphocytes and inhibiting neutrophils via actively synthesizing new proteins, blocking proliferation, and enhancing apoptosis as seen in *Figure 4*.

T lymphocytes: Glucocorticoids are known to induce apoptosis of double positive (CD4+/CD8+) thymocytes at physiological concentrations. In a study done by Pazirandeh et al. (2009) using transgenic mice with a conditional tetracycline-regulated expression of a transgenic rat glucocorticoid receptors (GR) in the thymocytes (hCD2-GR), they observed an increased number of GR receptors in their T cells. Glucocorticoids were shown to increase the thymic sensitivity to glucocorticoids while reducing the overall function of thymic cells. The same GR in T cells is required for survival of selection of said T cells. Without the GR present, the same T cells would undergo apoptosis. GR knockout (KO) mice were unable to repress the expression of cyclooxygenase (COX-2) leading to increased damage to gastrointestinal tract tissue but interestingly showed no response to diminished or canceled inflammation repression.

Myeloid cells: Myeloid cells include monocytes, macrophages, eosinophils, erythrocytes, and neutrophils. Eosinophils are one of the primary cells responsible for allergy responses. GR in eosinophils cells are responsible for glucocorticoid suppression of allergies from contact, such as poison oak or metal reactions, unlike T cells. Also, unlike T cells, deletion of myeloid cell GR canceled out inflammation repression caused by glucocorticoids.

In *neutrophils*, binding of the glucocorticoid to the GR results in synthesis of the protein annexin A1. This protein is responsible for the negative effect on COX-2 and phospholipase 2(PLA2), key contributors in promotion of inflammation, fever, and allergies. It also affects neutrophils by increasing the shredding of L- selectin while disrupting their adherence and emigration of the endothelium decreasing the number of neutrophils leaving the blood vessels (*Figure 3*).

Glucocorticoid treatment of obesity

Obesity and low-grade inflammation are often linked to each other and finding components that are able to reduce both would be major health benefit. Glucocorticoids are a contributing factor to metabolic syndrome. Increased glucocorticoid concentrations in plasma results in side effects including insulin resistance, weight gain, hyperphagia and hypertriglyceridemia (Wang, 2005). Glucocorticoid

receptor (GR) antagonists, such as mifepristone, can reduces both body fat and weight gain in patients with Cushing's syndrome and animals consuming a high-fat diet. Unfortunately mifepristone lacks any anti-inflammatory effects. Compounds which are able to be both a GR agonist, inhibit inflammation, as well as GR antagonist (improve metabolism) are a massive health benefit. Van den Huevel et al (2016) investigated the GR modulator C108297, which has been shown previously to have antagonistic and agonistic properties while not showing affinity for other steroid receptors. They compared this compound to mifepristone for known metabolic affects and then compared both to a vehicle control group. The mechanism for mifepristone is unclear, but previous study showed a potential to decrease weight gained on a diet meant to induce obesity (Asagami et al., 2011). The study used mice and separated them into 3 groups based on plasma triglyceride levels and their body weight. They were given 3 different diets so that at the completion of the study the levels for all 3 groups were the same (*Figure 5*). Methods of calculation were determining adipocyte size, indirect calorimetry, and plasma parameters. At the conclusion, C108297 reduced food and caloric intake and caused shift of consumption period to be more prevalent in the dark phase. C108297 treated mice displayed increased fat oxidation and decreased carbohydrate oxidation. Leukocytes were reduced as well as pro-inflammatory macrophages while increasing the anti-inflammatory macrophages. Expression of mRNA for the cytokines TNF-α and IL-1β was decreased while GILZ expression was increased. MKP1 and lipocortin1 levels showed no effect. These results all point to transrepression of pro-inflammatory genes while up-regulating the anti-inflammatory genes via selective modulation. Compounds like C108297 show promise in treating those who need anti-inflammatories and immunosuppressants as well as supporting treatment of obesity as seen in *Figure* 5.

Another key player in the treatment of obesity as well as stimulating anti-inflammatory molecules is physical exercise. Production of hypothalamic-pituitary-adrenal (HPA) can be stimulated by intense physical exercise, though the mechanism is not fully known. Both hypothalamic corticotropin releasing hormone (CRH) and arginine vasopressin play a role in exercise induced release of ACTH. Muscles send signals via neurons and humoral mediators (IL-6 and lactate) to the HPA system. A study done by Andrea Dovio et al. (2011) looked at urinary steroid profiles of 15 well trained healthy individuals in a structured workout setting. 11B-HSD type 1 activity was monitored by looking at its conjugated tetrahydrocortisone/urinary [alloTHF + tetrahydrocortisol (THF)] ratio while type 2 11B-HSD conjugated and unconjugated ratio were both measured. The cortisol secreted was measured using the sum of alloTHF, THF, total E (cortisone) and F (cortisol), and THE. This was the first study in humans to show

that intense physical exertement resulted in an acute increase of (alloTHF + THF)/THE ratio. It also looked at a ratio that includes both 11B-HSD1 activity as well as 11B-HSD2 which mediated the conversion of cortisol to cortisone. This occurs mainly in the kidney which has a reduced blood flow during physical exercise due to blood being redistributed to skeletal muscles.

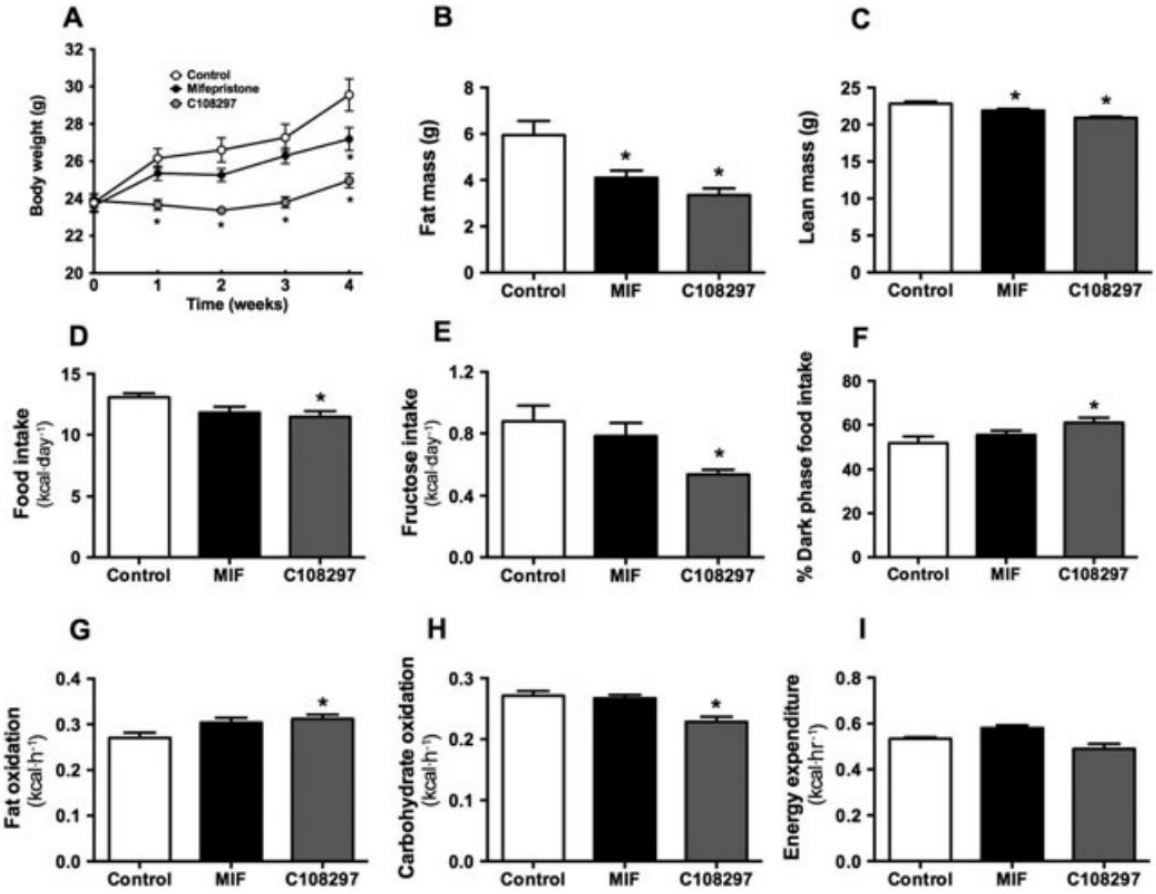

Figure 5. The figure above shows multiple graphs (A) Body weight. (B) fat mass and (C) lean mass post 4 weeks of diet treatment. Mifepristone increased energy expenditure as seen in graph I while C108297 decreased caloric intake as seen in Graph E. C108297 not only had similar effects to mifepristone in decreasing fat mass, but also increased fat oxidation and % dark phase food intake as seen in graphs G and F respectively.

A drawback was that the study doesn't look at 5a/5b reductase activity as it was not possible to distinguish between THF and alloTHF. Both (alloTHF + THF)/F and THE/E ratios had no change measured during the exercise sessions which gives strong support to the original hypothesis that there will be a net increase in the 11B-HSD1 systemically associated with exercise. Acute increases of cellular cortisol levels can be correlated to 11B-HSD activity and these increased levels allow for a shutdown of the

inflammation reaction in the muscle during exercise limiting muscle damage induced. Cortisol substrate (cortisone) is then able to freely diffuse back into myocytes from the vascular system.

Glucocorticoids have known functions associated with metabolism. Combating inflammation through their use can alleviate the symptoms but also indirectly correct the underlying cause in obesity. The expression of gluconeogenesis enzymes are enhanced in the presence of glucocorticoids stimulation of fat breakdown. Glucocorticoid treatment can be used to simultaneously both reduce pain and recovery time in the user, with the added benefit of increasing metabolism.

Chronic inflammation:

Acute inflammation results in acute release of ACTH and cortisol resulting in release of amino acids and lipids from extrahepatic tissue allowing for gluconeogenesis. It also redistributes the leukocytes. Chronic inflammation elevates ACTH and cortisol can lead to a decreased immune response to infectious agents leading to sepsis, or system wide infection. C. Edwards (1996) study showed that the liver reactivated the cortisone to cortisol as well as the kidney's role for degrading the cortisol back to cortisone to be excreted. During inflammation, the liver can surpass the production of cortisol in the adrenal gland due to the 11β-HSD type 1 activity. This leads to downregulation of ACTH due to elevated cortisol serum levels which can explain that, at a simple level, why cortisol production is not dependent on the brain-derived hormonal regulation. Edwards et al. (1996) study showed an increase in 11β-HSD2 activity in relation to 11β-HSD1 meaning synovial fibroblasts play a role in activating cortisol. When mixed with an increased ratio of lymphocytes and macrophages to fibroblasts, they saw more cortisol being degraded back to cortisone in rheumatoid arthritis (RA) compared to osteoarthritis (OA). This then opened up discussion for a therapy to block or interfere with the 11β-HSD type 1/2 in RA.

Application:

Glucocorticoids can be administered orally through pill or inhalation, topically, or via injection. For treatment of sport-related injuries, injection and oral administration are the most common routes of administration. For joint pain and injury, injection of the glucocorticoid into the joint space is the most prevalent form of treatment compared to a local anesthetic. A corticosteroid injection such as triamcinolone acetonide into the intra-articular space of the hip has been shown to not only decrease pain and inflammation, but also increase function and range of motion compared to a similar injection with a local anesthetic like mepivacaine. Patients injected with the corticosteroid saw their use of

analgesics daily drop from 40% pre-injection to 7.5% post injection (n=40). No significant improvement or pain relief was observed in the local anesthetic patients and all 40 patients withdrew before the 12 week follow up from lack of effect (Lorbach et al., 2010).

Oral administration is an alternative route some prefer due to its relative ease, practically no risk of infection and painless application compared to injection. There are some draw backs to this route as it will be applied systemically instead of concentrated to the area of interest. A study was done that looked at the comparison of shoulder scores and range of motion for both oral and intra-articular injections of prednisolone and triamcinolone respectively. The scoring was completed through two separate exams: visual analog scale (VAS) which measured pain of the patient and Constant-Murley Shoulder Outcome Score (CM) which measured the pain as well as ability to carry out everyday tasks (Lorbach et al., 2010). The shoulder scores results were superior for intra-articular CM scores compared to oral administration for all periods of follow-up as seen in *Figure 6* below. The VAS test though showed no significant difference between the two routes of administration for any time period. Range of motion was higher for intra-articular injection for flexion 4, 8, and 12 weeks follow-up as well as abduction 8 weeks, 6 and 12 months follow-up. External and internal rotation saw similar results with significant differences observed at 4, 8 (external), and 12 (internal) weeks.

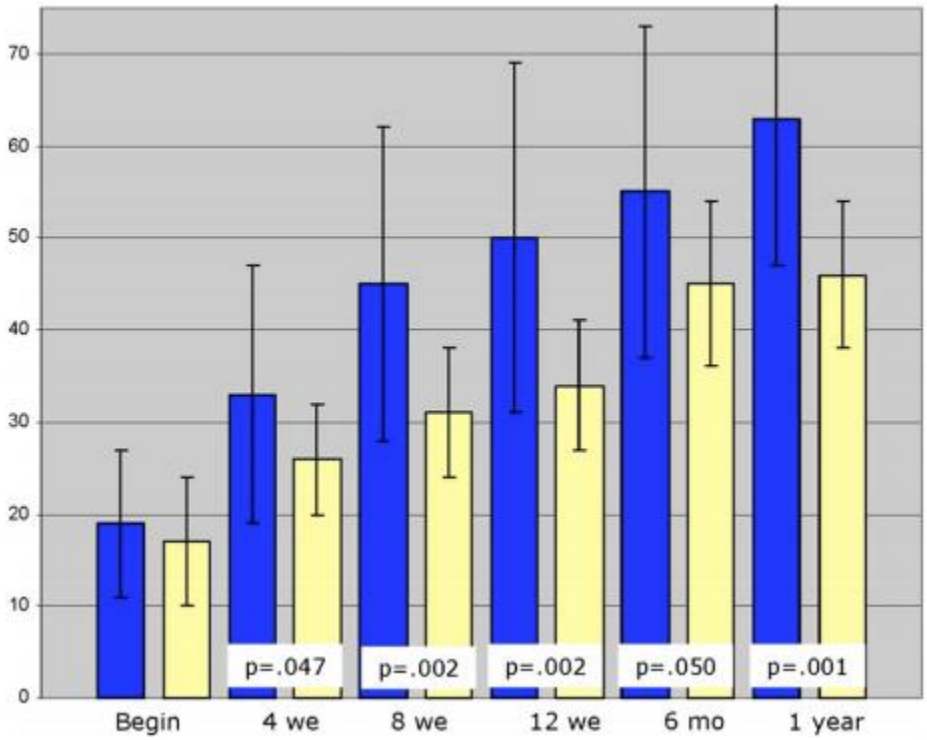

Figure 6. Results of oral glucocorticoid (yellow) vs. intra-articular treatment (blue) for the modified Constant and Murley score. Standard deviation bar included with the mean data.

Sport medicine:

Pubalgia, or groin pain related to sport injury, is present in 2-5 percent of all sport injuries. It is especially frequent in ice hockey and kicking sports such as soccer where the symphysis pubis and supporting musculature can be stressed from rotating or imposed differential load shift (Morelli V and Smith V, 2001). MRI has identified 3 different forms of symphysial derangement from which pain can arise including: micro tearing at the attachment of the adductor longus and rectus abdominis, osteitis pubis, and micro tearing of short adductor (gracilis, adductor brevis, and pectineus muscles) attachment. Applying glucocorticoid, specifically 80 mg of methylprednisolone, into the symphysial cleft and to the site which abnormality was identified resulted in after injection, 89% (n=40) reported improvement in pain and function after injection. The reduction in pain was sustained in 60% after a minimum 6 month period post-injection and 47% (n=21) reported complete resolution of symptoms after the injection. 43% (n=19) reported a partial improvement and the remaining 5 patients reported no effect from the injection.

Tendon rupture:

Though there has been no reported case of glucocorticoid injection directly resulting in tendon rupture, multiple reports of glucocorticoids indirectly contributing to tendon rupture exist. For example, a 55-year-old male presented with pain in his right hand dorsally. After cleansing the area with alcohol, two separate SC injections were given between metacarpophalangeal joints of the second, third, fourth, and fifth digits. Ten days later, a similar injection was given at the dorsal wrist joint region due to persistent pain being reported, though cleansing of the area of alcohol was not reported at that time point. After a period of two months, the patient returned with swelling and underwent surgery to drain the pus. The extensor tendons were observed and intact. 2 days later, the patient reported an absence of extensor function of digits 2, 3 and 4. After the wound was re-opened, it was observed that the extensor digitorum communis tendons were ruptured for digits 2 through 4. After infection subsided, the tendons were repaired. Multiple factors can be attributed to the rupture including: inadequate sterilization, diabetes causing impaired cellular immunity and angiopathy of small vessels, and administration of steroids. The latter result in collagen degeneration, weaken the tendon, and inhibit the repair. The

potential role of the glucocorticoid administration in the rupture of the tendon remains unclear but it cannot be ruled out as a contributory factor.

Conclusion:

The use of glucocorticoids in healthcare has been a revolutionary treatment option to athletes and exercising individuals. While not only being able to treat patients suffering from tumors and arthritis, their use in treating sport related injuries is huge. Binding to the GR and creating a complex, the glucocorticoid and receptor collectively travel to the nucleus and acts through transactivation and transrepression. As seen above, this can result in a wide variety of effects that can be useful to athletes and gym-goers alike.

The obesity treatment study gave great promise to the use of glucocorticoids outside the sports world reaching a much larger population in the avid gym attendee. Having the ability to decrease the inflammation shortening the recovery time while also being able to help with weight loss is extremely beneficial in our society which is predominantly obese. Spending billions of dollars each year fighting multiple diseases all attributed to obesity in some way such as heart disease and diabetes, it is research we need to continue to fund.

In sports and athletics, injuries ranging from groin pain to torn ligaments can all be treated with glucocorticoids. The benefits include a decreased cost and chance of infection while also limiting the trauma to the patient. The drawbacks are an unsure mechanism of success compared to surgery and also the risk of worsening the injury down the road. Cases such as the tendon rupture are few and far between but do highlight the potential of devastating injures resulting from intra-articular glucocorticoid injections. More studies are needed to observe the long-term effects of glucocorticoid treatment on ligament tear instead of surgery.

Bibliography:

1. Alangari AA. 2014. Corticosteroids in the treatment of acute asthma. Ann Thorac Med. 9(4):187-192.

2. Asagami T, Belanoff JK, Azuma J, Blasey CM, Clark RD, Tsao PS. 2011. Selective glucocorticoid receptor (gr-ii) antagonist reduces body weight gain in mice. J Nutr Metab. 2011:235389.

3. Auvinen HE, Coomans CP, Boon MR, Romijn JA, Biermasz NR, Meijer OC, Havekes LM, Smit JW, Rensen PC, Pereira AM. 2013. Glucocorticoid excess induces long-lasting changes in body composition in male c57bl/6j mice only with high-fat diet. Physiol Rep. 1(5):e00103.

4. Chandrasekaran S, Lodhia P, Suarez-Ahedo C, Vemula SP, Martin TJ, Domb BG. 2016. Symposium: Evidence for the use of intra-articular cortisone or hyaluronic acid injection in the hip. J Hip Preserv Surg. 3(1):5-15.

5. Choi H, McCartney M, Best TM. 2011. Treatment of osteitis pubis and osteomyelitis of the pubic symphysis in athletes: A systematic review. Br J Sports Med. 45(1):57-64.

6. Cole TJ, Blendy JA, Monaghan AP, Krieglstein K, Schmid W, Aguzzi A, Fantuzzi G, Hummler E, Unsicker K, Schütz G. 1995. Targeted disruption of the glucocorticoid receptor gene blocks adrenergic chromaffin cell development and severely retards lung maturation. Genes Dev. 9(13):1608-1621.

7. Coutinho AE, Chapman KE. 2011. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Mol Cell Endocrinol. 335(1):2-13.

8. Dietrich J, Rao K, Pastorino S, Kesari S. 2011. Corticosteroids in brain cancer patients: Benefits and pitfalls. Expert Rev Clin Pharmacol. 4(2):233-242.

9. Dovio A, Roveda E, Sciolla C, Montaruli A, Raffaelli A, Saba A, Calogiuri G, De Francia S, Borrione P, Salvadori P et al. 2010. Intense physical exercise increases systemic 11beta-hydroxysteroid dehydrogenase type 1 activity in healthy adult subjects. Eur J Appl Physiol. 108(4):681-687.

10. Edwards CR, Benediktsson R, Lindsay RS, Seckl JR. 1996. 11 beta-hydroxysteroid dehydrogenases: Key enzymes in determining tissue-specific glucocorticoid effects. Steroids. 61(4):263-269.

11. Gupte R, Muse GW, Chinenov Y, Adelman K, Rogatsky I. 2013. Glucocorticoid receptor represses proinflammatory genes at distinct steps of the transcription cycle. Proc Natl Acad Sci U S A. 110(36):14616-14621.

12. Lorbach O, Anagnostakos K, Scherf C, Seil R, Kohn D, Pape D. 2010. Nonoperative management of adhesive capsulitis of the shoulder: Oral cortisone application versus intra-articular cortisone injections. J Shoulder Elbow Surg. 19(2):172-179.

13. Morelli V, Smith V. 2001. Groin injuries in athletes. Am Fam Physician. 64(8):1405-1414.

14. Newton R. 2000. Molecular mechanisms of glucocorticoid action: What is important? Thorax. 55(7):603-613.

15. Patil RH, Naveen Kumar M, Kiran Kumar KM, Nagesh R, Kavya K, Babu RL, Ramesh GT, Chidananda Sharma S. 2018. Dexamethasone inhibits inflammatory response via down regulation of ap-1 transcription factor in human lung epithelial cells. Gene. 645:85-94.

16. Pazirandeh A, Jondal M, Okret S. 2005. Conditional expression of a glucocorticoid receptor transgene in thymocytes reveals a role for thymic-derived glucocorticoids in thymopoiesis in vivo. Endocrinology. 146(6):2501-2507.

17. Pitter KL, Tamagno I, Alikhanyan K, Hosni-Ahmed A, Pattwell SS, Donnola S, Dai C, Ozawa T, Chang M, Chan TA et al. 2016. Corticosteroids compromise survival in glioblastoma. Brain. 139(Pt 5):1458-1471.

18. Roth P, Happold C, Weller M. 2015. Corticosteroid use in neuro-oncology: An update. Neurooncol Pract. 2(1):6-12.

19. Scheidegger P, Weisskopf L, Hirschmüller A. 2017. Atraumatic bilateral rupture of the peroneus brevis tendon in recreational sport: A case report. SAGE Open Med Case Rep. 5:2050313X17745225.

20. van den Heuvel JK, Boon MR, van Hengel I, Peschier-van der Put E, van Beek L, van Harmelen V, van Dijk KW, Pereira AM, Hunt H, Belanoff JK et al. 2016. Identification of a selective glucocorticoid receptor modulator that prevents both diet-induced obesity and inflammation. Br J Pharmacol. 173(11):1793-1804.

21. Vandevyver S, Dejager L, Libert C. 2014. Comprehensive overview of the structure and regulation of the glucocorticoid receptor. Endocr Rev. 35(4):671-693.

22. Wang M. 2005. The role of glucocorticoid action in the pathophysiology of the metabolic syndrome. Nutr Metab (Lond). 2(1):3.

23. Woon CY, Phoon ES, Lee JY, Ng SW, Teoh LC. 2010. Hazards of steroid injection: Suppurative extensor tendon rupture. Indian J Plast Surg. 43(1):97-100.

24. Zhang J, Keenan C, Wang JH. 2013. The effects of dexamethasone on human patellar tendon stem cells: Implications for dexamethasone treatment of tendon injury. J Orthop Res. 31(1):105-110.